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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/359,975	07/23/99	WEINER	UPAP-0345

HM22/0226

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	18

DATE MAILED: 02/26/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/359,975	Applicant(s) Weiner et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Dec 11, 2000* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96, and 115-147* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96, and 115-147* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

1. Arguments set forth in Paper No. 9, filed December 11, 2000 regarding the rejection of claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-147 under 35 USC 112, first paragraph, enablement, have been considered but are not found convincing. Responses to the arguments are set forth in the repeated rejection below.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 58, 59, 63, 64, 67-72, 75, 76, 84-86, 94-96 and 115-147 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a pharmaceutical composition comprising DNA and a polynucleotide function enhancer and methods of immunization with the composition. While applicants have shown a composition comprising DNA and a polynucleotide function enhancer, they have not demonstrated any pharmaceutical application for the composition comprising DNA

and a polynucleotide function enhancer. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve demonstration that a composition comprising DNA and a polynucleotide function enhancer provides an immune response. It is known that production of an immune response is dependent upon a particular antigenic presentation and appropriate adjuvant. The identity of a specific antigen and demonstration of the immunogenicity of the specific antigen is not predictable, since each potential antigen must be tested to determine if it will elicit an immune response.

b- Only prophetic guidance and no examples are presented in the instant specification.

c- The nature of the invention is complex. The delivery of DNA to an animal for immunization and passive protection is a new and developing art as taught in Cho et al. at the abstract "[t]he factors essential for the successful development of this new claims of therapeutic agents are not necessarily the same as those for conventional small organic molecules" and at page 157, column 1 bottom, bridging to column 2, top "formidable transport and delivery problems are associated with macromolecular therapeutic agents. With all of these disadvantages, one might wonder why investigators remain so interested in the prospect of using

macromolecules as drugs. The answer lies in the potentially exquisite specificity that one can, at least theoretically, attain by using proteins or genes as therapeutic agents. The challenge is to convert the potentiality of macromolecular drugs into practical reality".

d- The prior art at the time of filing of the instant priority document Application No. 08/124,962, filed September 21, 1993, was teaching that it was unknown if DNA vaccines would be effective.

e- Those of skill in the art have taught the unpredictability of DNA vaccines. Rabinovich et al. taught at page 1401, column 3, "[t]he advent of recombinant DNA technology has stimulated the production and testing of new subunit vaccines designed to be safer and more efficient. Unfortunately, the limited immunogenicity of many of these candidates has hindered their development as potential vaccines. Strategies to enhance the immunogenicity of these candidate vaccines are therefore critical". Webster et al. taught at page 281 "[t]he ultimate vector for use in DNA immunization in humans and other animals, that will meet all of the above requirements, is clearly desirable, but has not yet been perfected. Plasmids for use in DNA immunization will continue to be refined in the coming years". Piscitelli et al. taught at page 68, column 2, bottom bridging to page 69, column 3, top, that those of skill in the art were still evaluating the use of DNA to produce an HIV immunization.

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Response to Arguments

4. Arguments set forth in Paper No. 9 assert that the instant invention is enabled because the production of an antibody is demonstration of immunization. The production of an antibody should not be confused with a production of immunity. Antibody production in animals has been routine for decades, but producing immunity by vaccination is not at all routine, and immunization is still a trial and error process.

5. Arguments assert in Paper No. 9 that examples 3, 28, 29, and 30 are working examples of DNA pharmaceutical compositions that produce an effective immune response in a mouse. These examples demonstrate that an immune response can be mounted against a peptide encoded by a viral sequence which has been tranfected into cells and subsequently expressed on the surface of the cells. Peptides expressed on cells have been used as targets for animal models of cellular immunity and humoral immunity for at least a decade. This, once again, does not demonstrate that the animal has been immunized against a pathogen, and is not a recognized animal model for immunity against a pathogen. Rabinovich et al. and Piscitelli et al. taught that the ability to produce an antibody in an animal by introduction of naked DNA was well known to those of skill in the art. The production of an antibody in an animal with naked DNA was not a demonstration of vaccination against a pathogen or a proliferative disorder.

6. Arguments assert in Paper No. 9 at Page 4, bottom bridging to the top of Page 5 that even though the instant specification fails to provide any working examples of the use a composition of DNA and bipuvacaine as claimed in the instant invention, that one of ordinary skill in the art

may use the teachings of the instant specification as guidance for the practice of the method. This issue is problematic, since Danko et al. (Gene Therapy, Vol. 1(2):114-121, 1994, see especially figure 3) teaches away from the co-administration of bipuvacaine and DNA. Danko et al. taught that bipuvacaine was effective only when administered at least 3 days prior the administration of the DNA. Similarly, the instant specification teaches the administration of bipuvacaine 24 hours in advance of the administration of DNA in working examples 3, 28 and 43. The instant specification provides only prophetic teaching of co-administration of bipuvacaine and DNA at page 27, line 15 bridging to page 29, line 34.

7. Arguments set forth in Paper No. 9 assert that Cho et al. taught "optimization" of the production of vaccines as cited at page 156, column 2, lines 6-12. With continued reading of the passage cited, Cho et al. goes on a lines 12-25 to emphasize the problems and some of the unknown factors which still face developers of the art. In short, Cho et al. do not teach "optimization" at all, but rather, a careful reading of the entire article makes the point that immunization with DNA is a developing and poorly understood art.

8. Arguments set forth in Paper No. 9 assert that this examiner alleges that the field of DNA immunization is unpredictable in general, even today. It is further asserted that this position is lacks evidence. While it is true that the field of DNA immunization is not well understood, even today, this examiner did not make that assertion in the repeated rejection above. But, for the record, Chattergoon et al., which is cited in Paper No. 9 as evidence that DNA technology is enabled, recites in the abstract "[e]xpression of these delivered genes has important

immunological consequences and **may** (emphasis added) result in the specific immune activation of the host against the novel expressed antigens. The recent demonstration by laboratories that these immune responses are protective **in some infectious disease experimental models** (emphasis added) as well as cancers **is viewed with cautious optimism** (emphasis added)....this technology will dramatically influence the production of **a new generation of experimental vaccines and immune therapies**" (emphasis added). It should be noted that the words are prophetic, and do not in any way state that there is certainty as to the outcome of any immunization.

9. Arguments set forth in Paper No. 9 assert that the invention is not a vaccine, but a pharmaceutical composition and a method for immunizing an individual, and a method for introducing DNA into cells of an individual. The only utility described in the instant specification for the instant claimed composition is the production of immunity to pathogens and proliferative disorders in an animal. Since this is the only utility described, the composition and methods have only one utility, namely, the production of immunity to pathogens and proliferative disorders in an animal by the introduction of a DNA into the cell of the animal (in other words, a vaccine). Therefore, the DNA composition is a vaccine.

10. Arguments set forth in Paper No. 9 cite Weiner et al. (Scientific American, 1999) as proof of the enablement of the DNA vaccine art. At pages 40-41 in the section entitled "Getting From Here To There", many of the enablement deficiencies cited in the rejection above are discussed along with the presentation of some inventive solutions to the problems of vaccination with

DNA. The tenor of the article is summarized at page 41, columns 2-3 "[a]s the years go by, the inherent manipulability of DNA should make it a vehicle of choice for teasing apart the body's complex immune responses to different disease-causing agents. With such information in hand, vaccine makers should be able to design vaccines that will channel immune responses down selected pathways. In the past, manufacturers had no way to custom-tailor their products easily and inexpensively. In the future, such "rationally" designed genetic vaccines are likely to provide new immune therapies for cancer and powerful ways to prevent or minimize any number of devilish infections that elude human control today". This makes it eminently clear that today's skilled artisan does not have the skill to effect an immune response by making an effective DNA vaccine.

11. Arguments set forth in Paper No. 9 assert that the passage cited in the above rejection addresses subunit vaccines, and that the instant invention is not drawn to subunit vaccines. The passage from Rabinovich et al. taught **DNA** subunit vaccines. Examples 43-56 of the instant specification use naked DNA subunit constructs to produce an immune response in an animal. While the claims are not drawn to DNA subunit vaccines, examples 43-56 are presented in the specification as evidence of enablement of the instant invention. If the instant examples 43-56 do not pertain to the instant claimed invention, then it should be so stated. At such time as it is clear that DNA subunit vaccines are not being contemplated as claimed subject matter then the rejection will be so amended to reflect that position.

12. Arguments set forth in Paper No. 9 assert that Webster et al. taught the successful introduction of DNA into an animal and the successful production of an antibody to the expressed product of the introduced DNA in the animal. Once again, the production of an antibody in an animal does not per se produce an immunity to a disease or disorder. The argument is therefore not found convincing.

13. Arguments set forth in Paper No. 9 assert that Piscitelli et al. taught the successful production of an antibody to an HIV protein in an animal. Once again, the production of an antibody in an animal does not per se produce an immunity to a disease or disorder. The argument is therefore not found convincing.

14. It is further argued in Paper No. 9 that it is "very likely that humans can also be effectively immunized with AIDS antigens without undue experimentation". Once again, the production of an antibody in an animal does not per se produce an immunity to a disease or disorder. As shown in the cited art of the above rejection, and repeated in the Chattergoon et al. and Weiner et al. references, the state of the art shows that one of skill in the art cannot make and use a DNA vaccine without a significant amount of non-routine experimentation. The argument is therefore not found convincing.

15. Finally, it is argued in Paper No. 9 that the Wands analysis of the above rejection is flawed because each factor has not been properly analyzed individually. The argument is made that "undue experimentation" is the key to the argument of each section. The above analysis does indeed follow the Wands factors, as set forth in sections a) through f). Each factor is

addressed with references which fully support the arguments. This fact is clearly made in the above responses to the arguments set forth in Paper No. 9. The key element of "undue experimentation" is the linchpin of enablement, and as such, has been emphasized in the rejection. Reference to "undue experimentation" in the rejection emphasizes the fact that "undue experimentation" is necessary to practice the claimed invention and is deemed to be an obvious, albeit reiterated point.

Conclusion

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of

such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.

Examiner

February 16, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER